99-C-0125: Osteosarcoma: Outcome of Therapy Based on Histologic Response. A Collaborative Effort of the POB/NCI, Texas Children's Hospital and University of Oklahoma.

In this pilot study, patients with newly diagnosed osteosarcoma will receive cisplatin/ doxorubicin/methotrexate in the neoadjuvant setting. Patients with non-metastatic disease and good response to neoadjuvant therapy will receive additional courses of cisplatin/doxorubicin/methotrexate in the post-surgical setting. Currently, three groups of patients with poor outcome can be identified: 1) metastatic disease, 2) unresectable disease and 3) nonmetastatic disease with poor response to neoadjuvant therapy. Therapy will be intensified with three courses of melphalan/cyclophosphamide in the adjuvant setting for these patients.

Eligibilty Criteria:

- **Age:** ≤ 25 years
- **Histologic Diagnosis:**

Part I:

- Histologically proven newly diagnosed osteosarcoma (patients with biopsy obtained at institutions other than NIH are eligible).
- non-metastatic high-grade osteosarcoma of bone
- patients w/metastatic disease &/or unresectable primary disease are eligible. Metastatic disease should be biopsy-proven. It is recommended that any lung lesion seen on chest CT >0.5 cm should be biopsied before designating it as metastatic disease. Thoracotomies are recommended for assessment.

Part II:

- Patients w/recurrent &/or progressive disease during or after therapy based on other treatment protocols which did not include cyclophosphamide and/or melphalan will be eligible for the arm containing cyclophosphamide/melphalan with stem cell rescue. Attempts to make them disease-free with surgery prior to high-dose chemotherapy is strongly encouraged.
- **Hematologic function:** Adequate bone marrow function with an ANC $\geq$ 1000/mm^3, platelet count $\geq$100,000 mm^3 (transfusion independent) and hemoglobin > 8.0 g/dl .
- **Renal function:** adequate renal function with serum creatinine ≤1.5x normal and creatinine clearance or radioisotope GFR>70 ml/min/1.73 m^2.
- **Hepatic function:** total bilirubin ≤ 2.0 mg/dl; ALT < 5x normal
- **Cardiac function:** ECHO or MUGA (SF≥27% or EF≥45%)
- **Informed consent**: All patients or their legal guardians (if the patient is less than 18 years of age) must sign a document of informed consent indicating their awareness of the investigational nature and the risks of the study. When appropriate the patient will be included in all discussions in order to obtain assent. Consent for reseach imaging will be obtained for those patients who agree to research imaging.

Exclusion Criteria:

- Osteosarcoma secondary to radiation or that arising from premalignant conditions
- Pregnancy
- Low-grade osteosarcoma, parosteal or periosteal osteosarcoma

- Patients who are cureently receiving chemotherapy on other protocols or treatment plans with no evidence of progressive disease are not eligible for any part of this protocol.

Pretreatment evaluation:

- History and Physical
- Labs: CBC/diff, platelets, Na, K, Cl, CO2, BUN, serum glucose, serum creatinine, serum bilirubin, alkaline phosphatase, SGPT, SGOT, LDH, Mg, Ca, phosphorus, uric acid, urine HCG for females of child-bearing age, CMV serology, GFR or 24 hour urine for creatinine clearance. Patients who are having stem cells collected require TV panel within 30 days prior to the collection procedure.
- Imaging Studies: plain films of primary, CT scan of primary, MRI of primary (if local control was amputation or limb salvage, MRI is at discretion of investigator), CXR, chest CT, bone scan.
- MUGA or 2D-ECHO
- Audiogram: Part I only
- Research Imaging: for patients entering Part I only: DEMRI of primary for patients who sonsent to this research imaging study
- Central line placment

GENERAL TREATMENT PLAN:

- Patients treated on Part I:
- Treat with cisplatin and doxubicin w/dexrazoxane for 2 courses at weeks 0,5 and methotrexate on weeks 3,4 and 8,9.
- Patients who have consented to research imaging will have repeat DEMRI studies prior to surgery
- Surgery at Week 11; if unresectable, see Part II.
- Patients with ≥90% necrosis will continue therapy with cisplatin , doxorubicin with dexrazoxane and high dose methotrexate.
- Patients with < 90% necrosis, or those entering Part II, see below.
- Patients who are treated on Part II (<90% necrosis at surgery, unresectable primary, metastatic at presentation, recurrent &/or progressive disease): will receive 3 courses of cyclophosamide and melaphalan with peripheral stem cell support. These 3 courses are given 4 weeks apart.
- If <90% necrosis at surgery, patients will be treated with 3 courses of cyclophosphamide and melphalan with peripheral stem cell support.
- If unresectable primary: treat with 3 courses of cyclophosphamide and melphalan with peripheral stem cell support after reevaluation following neoadjuvant therapy.
- All patients w/newly diagnosed metastatic disease, will undergo surgery after neoadjuvant chemotherapy for local control of the tumor and removal of all metastatic sties when feasible. Following neoadjuvant chemotherapy and definitive surgery, all patients with metastatic disease at diagnosis will receive high-dose cyclophosphamide and melphalan with peripheral stem cell support.
- Patients with recurrent and/or progressive disease during or after therapy based on other treatment protocols which did not include cyclophosphamide and/or melphalan will be treated with 3 courses of cyclophosphamide and melphalan with peripheral stem cell support.

- Filgrastim (5 μg/kg) will be administered subcutaneously daily beginning 24 hours after completion of chemotherapy and continued:

Part I:

Until ANC>5000/mm^3 on 2 separate determinations (at least 24 hours apart).

Filgrastim not required for weeks 24 and 29 (on patients w/≥90% necrosis).

Part II:

For at least 7 days or until the ANC > 2000/mm^3 for at least 2 consecutivve days.

CORRELATIVE STUDIES:

- Tumor Biology: tumor tissue will be processed for development of cell lines and murine xenotransplant models.

ACCRUAL:

- The trial is approved and open for patient accrual. Please call Donna Bernstein 301-435-7804, Lauren Long 301-496-0486 or Dr. Lee Helman at 301-496-4257. Other participating centers are Texas Children's Hospital, Cook Children's Hospital and Univesity of Oklahoma Health Sciences Center.